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Re-irradiation with concurrent and maintenance nivolumab in locally recurrent and inoperable squamous cell carcinoma of the head and neck: A single-center cohort study

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ABSTRACT

Background: The rate of loco-regional recurrences for locally advanced head and neck squamous cell carcinoma (HNSCC) following standard treatment reaches up to 50%, accompanied by a probability of 20% to develop a second primary tumor in the head and neck region.
Methods: Ten patients with inoperable, in-field recurrence of HNSCC following previous primary or adjuvant radiotherapy (RT) in combination with concurrent platinum-based chemotherapy were re-irradiated with 60 Gray in 30 fractions between December 2017 and January 2020 with concurrent and maintenance nivolumab administration. Data were retrospectively collected and compared with patients who underwent re-irradiation (ReRT) with concurrent cisplatin following propensity score matching (PSM). Local progression-free survival (LPFS) and overall survival (OS) were visualized using Kaplan-Meier method (log-rank test).
Results: All patients completed ReRT. Median number of applied courses of nivolumab was 12 (range, 3–38). OS rate was 50% at 12 months and the median OS was 11 (range, 2–23) months. Six and 12 month LPFS rates were 60% and 30%, respectively. Median LPFS was 8 (range, 2–19) months. OS and LPFS rates were not inferior to those of patients treated with concurrent cisplatin. No unexpected radiation-related toxicity occurred. A total of four patients developed any-grade immune-related adverse events of which two presented with grade 3 toxicities. One patient died within 3 weeks after ReRT. Higher blood levels of CRP ($p = 0.004$), lower levels of hemoglobin ($p = 0.029$) and higher neutrophil/lymphocyte ratio ($p = 0.004$) were associated with impaired LPFS. Higher recursive portioning analysis (RPA) class was associated with impaired LPFS ($p = 0.022$) and OS ($p = 0.024$).
Conclusion: The combination of ReRT and nivolumab for locally recurrent HNSCC was feasible without occurrence of unexpected toxicities. Combined radioimmunotherapy might offer an effective treatment option for carefully selected pre-irradiated patients ineligible for salvage surgery.

1. Introduction

Despite advances in surgical techniques, radiotherapy (RT) application and chemotherapy (CHT) in terms of available agents and schedules, the rate of loco-regional recurrences for locally

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advanced head and neck squamous cell carcinoma (LA-HNSCC) reaches up to 50%, accompanied by a probability of about 20% to develop a second primary tumor (SPT) in the head and neck region [1–3]. In case of loco-regional recurrence, survival is limited with best supportive care (BSC) [4]. If possible, salvage surgery is standard of care (SOC) with 5-year overall survival (OS) rates up to 39% [5]. However, only about every fifth patient is suitable for this treatment approach [6]. The preferred, sole systemic therapy option for this patient population has been the EXTREME protocol for about ten years with objective response rates of 36% and a median OS of about one year [7]. In 2019, the combination of cisplatin, 5-fluorouracil (5FU) and pembrolizumab or pembrolizumab alone [8] replaced EXTREME as the new first-line systemic treatment for all recurrent/metastatic patients or patients with combined positive score (CPS) of ≥ 1, respectively.

For recurrent and/or metastatic (R/M) HNSCC patients unsuitable for surgery, ReRT offers a potentially curative treatment besides palliative systemic options as described above [7,9–13]. Nivolumab gained approval in 2016 by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for R/M HNSCC after platinum-based chemotherapy following the results of the Checkmate 141 trial in 2016 [14] and has become the preferential agent for platinum-refractory patients. The combination of nivolumab with ReRT has not been studied so far.

This study investigated the feasibility, toxicity and efficacy of ReRT in combination with nivolumab for patients with loco-regional recurrent and inoperable HNSCC.

2. Patients and methods

2.1. Patients and eligibility criteria

This study reports on ten patients treated with ReRT and nivolumab between 2017 and 2020 at the Department of Radiotherapy and Oncology and the Department of Medical Oncology of the University Hospital Frankfurt, Germany. Data were retrospectively collected and analyzed following institutional ethics board approval (SKH-3-19, 4/09) in accordance with the Declaration of Helsinki in its actual, revised form. All patients provided written informed consent for their designated treatments.

The patient selection for the treatment with ReRT and nivolumab was based on the following criteria: Firstly, the patient had an inoperable, in-field recurrence of HNSCC following previous primary or adjuvant RT with concurrent platinum-based (cis-/carboplatin) CHT. Secondly, the time interval between primary RT and ReRT was at least 6 months. Thirdly, considering the localized tumor burden, the interdisciplinary tumor conference voted for ReRT in combination with nivolumab instead of palliative polychemotherapy. Fourthly, the patient did not receive nivolumab or any other immunotherapy (IT) or targeted therapy (TT) before. Fifthly, the patient did not have a history of autoimmune disease or active infectious disease. Sixthly, the patient had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of ≤ 2. Seventhly, the tumor recurrence did not surround the carotid arteries by more than 180° or showed radiological signs of carotid-infiltration. Reasons for the decision for nivolumab as systemic treatment were as follows: Firstly, re-challenge with platinum-based therapy is not an evidence-based approach, having an unfavorable side effect profile. Secondly, other systemic monotherapies were inferior to nivolumab according to the Checkmate 141 trial results. Patient assessment furthermore included the following tools: Charlson Comorbity Index (CCI) [15], the revised Head and Neck Charlson Comorbity Index (HN-CCI) [16], and the Recursive Partitioning Analysis (RPA) [17]. The RPA classification was defined upon a multicenter, retrospective cohort of 412 patients who underwent ReRT. Factors associated with OS were included into the model resulting in three distinct classes for the purpose of OS estimation: Those >2 years from the first treatment with resected tumors regardless of final margin status (Class I, 2-year OS 61.9%), those >2 years out with unresected tumors or <2 years out without organ dysfunction (Class II, 2-year OS 40.0%), or those <2 years or less from the previous course with organ dysfunction (Class III, 2-year OS 16.8%).

2.2. Pre-treatment workup

Pretreatment evaluation included complete patient history, physical examination and computed tomography (CT), magnetic resonance imaging (MRI) of the neck and/or positron emission tomography in combination with CT (PET-CT). Staging included CT of thorax and abdomen for patients without PET-CT. All recurrences were histologically confirmed.

2.3. Radiotherapy

All patients were irradiated in supine position. Customized thermoplastic treatment masks were used for immobilization during planning CT and treatment. Fusion of planning CT images (3 mm slice thickness) with pretreatment diagnostic imaging was performed. Gross tumor volume (GTV) to planned target volume (PTV) expansion was as follows: GTV to clinical target volume (CTV): 5 mm, cropped for anatomical margins; CTV to PTV: 5 mm. The prescribed dose was 60 Gray (Gy) for all patients in 30 daily fractions which has commonly been recommended in the ReRT setting [18]. RT was delivered by a linear accelerator using 6MV photons as intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT). Focal cumulative spinal cord maximum doses (Dmax) were kept to a maximum of 67.5 Gy, assuming a maximal tolerance of 45 Gy for the spinal cord and at least 50% recovery of the neural tissue after a time interval of at least 6 months [19-22]. No dose limits were considered for other tissues.

2.4. Nivolumab administration

According to nivolumab approval, patients received either 3 mg/kg every two weeks (q2w, patients no. 1–5) or 240 mg fixed dose (FD, patients no. 6–10) q2w. First administration was applied within the first two weeks of ReRT, repeated two more times during ReRT, and continued afterwards until tumor progression or higher grade toxicity. During treatment, patients were monitored clinically for toxicity every week, and underwent laboratory examinations every second week with differential blood count, metabolic panels including liver and kidney function, serum electrolytes, thyroid function and inflammatory parameters. Decisions regarding toxicity management and temporary or permanent treatment discontinuation strictly followed guidelines from the European Society for Medical Oncology (ESMO) [23].

2.5. Propensity score matching and correlation cohort

Propensity score matching (PSM) was performed using the package "MatchIt" of the software R (The R Foundation for Statistical Computing, v3.5.0, Vienna, Austria). Variables included in the PS were as follows: gender, age, ReRT PTV size, time between radiotherapies, and ReRT doses. PS distributions are shown in supplementary Table A1. Patient-, treatment-, and outcome-characteristics of the correlation cohort treated with ReRT and cisplatin were retrospectively retrieved from a prior study of our group [21].

2.6. Analysis

Tumor staging was documented according to the UICC (Union international contre le cancer). Tumors were staged according to the TNM classification of malignant tumors in its respectively current version by the time of treatment [24]. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) in its respectively current version by the time of treatment. Baseline toxicity was assessed before ReRT, weekly during RT, every two weeks during nivolumab maintenance therapy and every three months after discontinuation. Efficacy was assessed by restaging via clinical examinations every two to three months and imaging utilizing CT or MRI scans of the head and neck and CT of thorax and abdomen during and after treatment every three months. Treatment response was assessed using response evaluation criteria in solid tumors (RECIST) [25]. Differences between categorial variables were assessed by the Pearson chi-squared test. Overall Survival (OS) was measured from diagnosis of recurrence until death of any cause. Local progression-free survival (LPFS) was measured from diagnosis of recurrence until occurrence of local progression or death from any cause. Patients who were alive and/or event-free were censored at last contact. Survival estimates were visualized using Kaplan-Meier method. The following median pre-treatment values were used to dichotomize clinical variables for analyzing their association with outcome following radioimmunotherapy (RIT): C-reactive protein (CRP, median: 2.5 mg/dl, range 0.1–7.0), hemoglobin (HB, median: 12.8 g/dl, range 10.7–14.9), thrombocytes (median: 299.5/nl, range 181.0–415.0), leukocytes (median: 8.4/nl, range 4.9–14.9), body-mass index (BMI, median: 22.5 kg/m^2 body surface area (BSA), range 18.0–28.0), ratio of neutrophil granulocytes to lymphocytes (NLR, median 6.5, range 1.4–32.1), PTV size (median: 83.1 cm^3, range 33.5–164.3). Analyses were performed using SPSS (IBM SPSS Statistics, v24.0, Armonk, NY, USA). Statistical significance was considered at $p < 0.05$.

3. Results

3.1. Initial patient characteristics and primary treatment

Ten patients were included for analysis with first tumor diagnosis between January 2009 and November 2017. Of these, nine patients were men and the median age was 63 (range, 46–71) years by the time of initial tumor diagnosis. Seven patients had a history of smoking and five of alcohol abuse. Nine patients had an ECOG-PS of 0. CCI amounted to a total score of 2 for eight patients due to their malignant tumor disease. Primary tumor sites were oropharynx in four cases, oral cavity in two cases, hypopharynx in two cases, and larynx and maxillary sinus in one case. Eight patients had received primary chemoradiotherpy (CRT) for LA-HNSCC and 2 patients postoperative CRT. Concurrent systemic therapy consisted of platinum-based agents in all cases. Median prescribed radiation doses for the primary tumor region were 70.6 (range, 70.0–72.0) Gy in the definitive and 64.8 Gy in the adjuvant/additive setting (supplementary Table A2).

3.2. Comorbidity status, recurrence and re-irradiation

ECOG-PS worsened in 40.0% of patients between initial tumor diagnosis and diagnosis of the latest recurrence. CCI and HN-CCI did not decrease in any case between the RT treatments. Two patients were classified into RPA class I, six into class II and two into III prior to ReRT. Eight recurrences developed within the prior high-dose volume and median time interval between the RT treatments was 27.5 (range, 11–119) months. Patients were treated by ReRT between December 2017 and January 2020. Median size of the ReRT PTV was 83.1 (range, 35.5–159.5) cm^3 and median prescribed cumulative maximal RT dose to the ReRT PTV was 127.4 (range, 116.0–130.6) Gy. All patients completed ReRT with 60 Gy in 30 fractions as scheduled without interruptions (Table 1A).

3.3. Radiation exposure to organs at risk and RT related adverse events

During treatment planning, focal Dmax constraint for the spinal cord was kept to 67.5 Gy. No other dose maximum dose constraints were considered (supplementary Table A3). Following initial RT, one patient suffered from chronic grade 3 dysphagia, one from grade 3 chronic leukocytopenia, and one patient developed grade 3 osteoradionecrosis requiring surgical decortication. After ReRT, a total of three patients suffered from grade 3 chronic dysphagia leading to feeding tube dependency. Furthermore, most patients suffered from grade 1–2 pain, mucositis and dermatitis during both primary RT and ReRT, whereas anemia was the most prevalent hematologic toxicity in both treatments (supplementary Table A4).

3.4. Treatment characteristics and adverse events of nivolumab

According to nivolumab approval by that time, the first five patients received 3 mg/m^2 BSA q2w (median 168, range 156–240 mg) of nivolumab and the following patients 240 mg FD q2w. Patients outcome was not affected by nivolumab administration regimen (LPFS: $p = 0.369$; OS: $p = 0.430$). Median number of applied courses of nivolumab was 12 (range, 3–38). By the time of data cut-off in March 2020, the treatment of three patients was ongoing. Treatment was discontinued due to toxicity in two cases, progressive disease (PD) in four cases and death in one case. After nivolumab termination two patients received another therapy whereas four patients received BSC. Of the patients available for response-evaluation 28.6% showed complete response (CR), 14.3% partial response (PR) and 57.1% PD by the time of their last visit. A total of five patients were diagnosed with PD in terms of local progression without signs of distant metastases until the end of follow-up (Table 1B). Exemplary MRI scans of therapy response to RIT are shown in Fig. 1. A total of four patients developed any-grade immune-related adverse events (irAE) of which two patients experienced grade 3 toxicities (Table 2). Occurrence of high-grade irAE did not affect outcome (LPFS: $p = 0.809$; OS: $p = 0.675$). One patient (no. 9) died three weeks after completion of ReRT.

3.5. Outcome and association of pre-treatment clinical factors with LPFS and OS

Median follow-up from diagnosis of recurrence for the total cohort was 11 months (range, 2–23). Twelve-month OS rate was 50% with a median OS of 11 (range, 2–23) months. Five patients died during follow-up. Furthermore, five patients were diagnosed with PD. Six and 12 month LPFS rates were 60% and 30%, respectively. Median LPFS was 8 (range, 2–19) months. Programmed cell death ligand 1 (PD-L1) status according to the tumor proportion score (TPS, $\geq$1 vs. <1 [14]) was not associated with outcome within this cohort (Table 1B, Fig. 2). No patient developed distant metastases during follow up. Accordingly, the study omitted survival analyses for distant metastases-free survival (DMFS) and progression-free survival (PFS) was identical with LPFS. Higher blood levels of CRP ($p = 0.004$), lower levels of hemoglobin ($p = 0.029$), higher NLR ($p = 0.004$) and a higher RPA class ($p = 0.022$) were associated with impaired LPFS (Fig. 3) whereas ECOG-PS, BMI, leukocytes and thrombocytes levels were not asso-

Table 1A
Comorbidity status, recurrence and re-irradiation characteristics.

Patient No.	ECOG-PS/CCI/HN-CCI/ RPA class	rTrN, G, (all M0)	Time interval between RT courses (months)	PTV Re-RT (cm^3)	Site of recurrence (prior PTV)	Cumulative PTV dose Re-RT (Gy, according to prescription)
1	2/4/0/II	T3 N0, G2	86	93,6	PTV1	124,8
2	0/5/0/III	T3 N0, G2	18	81,8	PTV1	130,6
3	0/3/0/II	T3 N0, G3	96	68,2	PTV1	124,8
4	2/6/0/I	T3 N2c, G2	36	159,5	PTV3	116,0
5	1/9/2/II	T2 N0, G2	14	112,8	PTV1	130,6
6	0/4/0/II	T0 N1, G3	32	35,5	PTV2	130,6
7	1/6/0/II	T3 N0, G3	11	164,3	PTV2	119,4
8	0/3/0/I	T2 N0, G2	119	78,4	PTV2	119,4
9	1/9/0/III	T3 N0, G2	23	83,1	PTV1	130,6
10	0/3/0/II	T3 N0, G2	21	95,6	PTV1	130,0

Abbreviations: CCI – Charlson comorbidity index, HN-CCI – Head and neck Charlson comorbidity index, RPA - recursive partitioning analysis, Re-RT – Re-irradiation, IMRT – intensity-modulated radiotherapy, VMAT – volumetric modulated arc therapy, PTV – Planned target volume.

Table 1B
Characteristics of nivolumab treatment.

Patient No.	TPS (%), CPS score	No. applied Nivolumab courses; absolute dose* (mg)	Reason for termination of Nivolumab	Therapy following Nivolumab	Last local control
1	40, 41	11 (156)	Toxicity (hypothyreosis)	BSC	CR
2	0, 1	9 (168)	PD	BSC	PD
3	30, 31	14 (165)	Toxicity (hypothyreosis)	BSC	PD
4	10, 20	19 (240)	PD	Surgery	PD
5	0, 10	8 (240)	PD	BSC	PD
6	0, 0.5	38 (240)	Treatment ongoing	NA	CR
7	99, 100	13 (240)	PD	EXTREME	PD
8	0.5, 1	22 (240)	Treatment ongoing	NA	PR
9	0.5, 1	3 (240)	Death	NA	NA
10	0, 1	4 (240)	Treatment ongoing	NA	NA

Abbreviations: TPS – Tumor proportion score, CPS – combined positive score, CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease, EXTREME – cisplatin, 5-fluouracil, cetuximab, BSC – best supportive care.
Note: *According to first prescription.

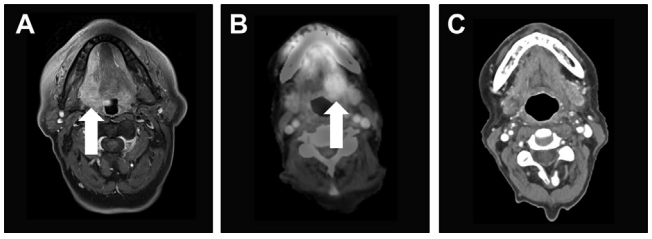

Fig. 1. Exemplary imaging of patient no. 7. A: Primary diagnosis of oropharynx carcinoma (MRI, T1 weighted + intravenous contrast medium); B: Diagnosis of loco-regional tumor recurrence (Fluorodeoxyglucose PET-CT); C: Twelve months follow-up without tumor detection (CT + intravenous contrast medium).

Table 2
Treatment related adverse events during nivolumab therapy.

Adverse effects	Treatment related adverse events during nivolumab therapy (No. patients)	
Grade	**1–2**	**3**
Hypothyreosis	1	2
Hyperthyreosis	1	0
Colitis	2	0
Athralgia	1	0
Pancreatitis	1	0
Rash	1	0

ciated with LPFS (supplementary fig. A1). Regarding OS, only increased RPA class was associated with impaired outcome (supplementary fig. A2). PTV size was not associated with LPFS and OS (both p = 0.299).

3.6. Comparison of adverse effects and outcome from ReRT with nivolumab or cisplatin

PSM resulted in the matching with ten patients treated with ReRT and cisplatin. Their characteristics are shown in (supplementary Table A5). Subsequent analysis revealed no differences regarding radiation-related toxicity and outcome when compared to the nivolumab group investigated in this study (supplementary Table A6; supplementary fig. A3).

4. Discussion

To the best of our knowledge, this study reports the first results of a combined second in-field-irradiation with programmed cell death protein 1 (PD-1) inhibition for locally recurrent, inoperable head and neck cancer. For R/M HNSCC patients unsuitable for surgery, ReRT offers a feasible, and potentially curative treatment also in combination with CHT besides palliative systemic options [7,9–13,19,20,26]. Feasibility of external-beam ReRT in combination with CHT has been demonstrated within several prospective clinical trials [19,20,26], however these trials were characterized by a low proportion of patients with prior CHT, split-course regimens and relatively low cumulative RT-doses, as well as high toxicity and treatment-related death rates. Regarding ReRT utilizing IMRT, several retrospective, single institutional studies with or without concurrent CHT exist [9], whereas prospective data collection in this setting is limited [19,27]. The use of cisplatin in these studies primarily resulted in higher toxicity rates rather than improved outcome [10–12,19]. When compared to a matched cohort of patients receiving ReRT in combination with cisplatin, the outcome

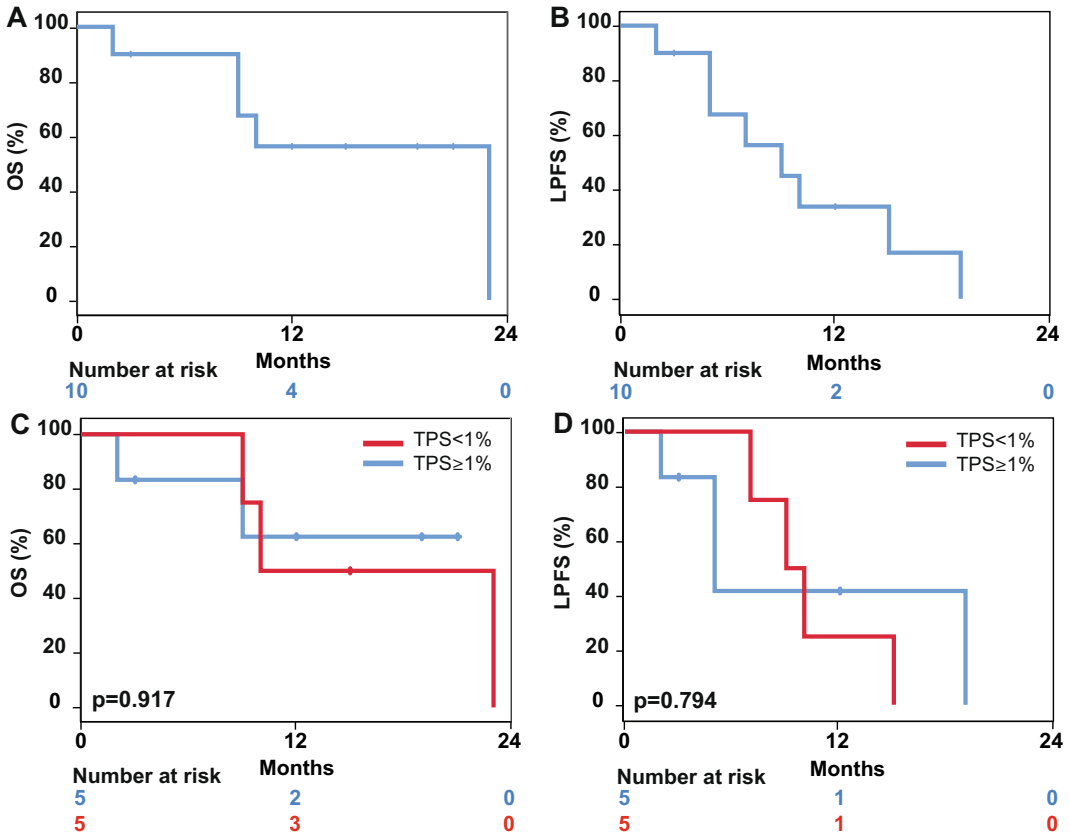

Fig. 2. Oncological outcome. A: Overall survival from recurrence treated by re-irradiation and nivolumab; B: Local progression-free survival from recurrence treated by re-irradiation and nivolumab; C: Overall survival from recurrence treated by re-irradiation and nivolumab according to PD-L1 status; D: Local progression-free survival from recurrence treated by re-irradiation and nivolumab according to PD-L1 status. Abbreviations: OS – Overall survival, LPFS – Local progression-free survival, TPS – Tumor proportion score; Nivo – Nivolumab.

of this cohort was not inferior with similar ReRT-associated toxicities.

ReRT late grade ≥3 toxicity rates range, according to the literature, between 15% and 48% for IMRT, with 1–11% treatment-related deaths [9,28]. In our cohort, overall RT related late grade 3 toxicity rate was 20%, consisting solely of dysphagia. One of these patients suffered from grade 3 dysphagia already before ReRT. No grade 4 toxicities have been observed. One of the largest patient series receiving intensity-modulated ReRT was reported by the MIRI collaborative [17,18,28]. The authors reported a severe grade late toxicity rate of 16.7%. However, ReRT doses and PTV sizes were inhomogeneous. A single patient from our cohort (no. 9) with serious comorbidities, including diabetes, died within 3 weeks after ReRT. He was admitted to another hospital one week after ReRT completion due to symptomatic hyperglycemia. In the course of hospitalization, the patient suffered from progressive vigilance reduction. Blood sugar levels were corrected and cerebral CT scans and thyroid parameters did not reveal abnormalities. However, a direct relation with the treatment cannot ultimately be ruled out.

Currently, nivolumab has been approved as systemic therapy following any prior platinum-based CHT for R/M HNSCC, without any limitations regarding time-interval to previous treatment, following the results of the Checkmate 141 trial. Accompanied by lower rates of grade 3–4 toxicities, nivolumab showed superior OS rates when compared to SOC monotherapies for patients with or without PD-L1 expression [14]. Median PFS within the Checkmate 141 trial with nivolumab monotherapy was 2.0 months and OS was 7.5 months (12 month-OS rate: 36%) with an overall response rate (ORR) of 13.3Pembrolizumab was tested as treatment for R/M HNSCC following platinum-based therapy within the Keynote-040 trial. PFS was 2.1 months and OS 8.4 months (12-month OS rate: 37%) with an ORR of 14.6% [29].

Taking into account the circumstances that a cross-comparison between studies is difficult and also the low patient number in our cohort, combined RIT in our study achieved superior OS rates when compared to IT alone in the overall cohorts Checkmate 141 and Keynote-040 trials. Also, the exact numbers for patients with isolated local tumor recurrence were not available for these trials further hampering the outcome comparison. Therefore, it has to be emphasized that no metastasized patients were included in the present study and all patients received IT as first-line palliative treatment following platinum-based CHT in the primary situation. The Keynote-048 phase III trial already introduced above reported of a median PFS of 2.3–3.4 months across all populations, with a median OS of 11.5 months at final analysis [8]).

With PD-1 and PD-L1 inhibitors being available, several phase 2/3 trials for R/M HNSCC are ongoing or completed, whereas only one phase 3 trial for the primary treatment of HNSCC combining RT and IT reported detailed results so far [30,31]: a large phase III trial investigating avelumab vs. placebo in combination with primary CRT with 70 Gy and cisplatin was terminated following an interim-analysis because of inefficacy [32,33]. However, phase 1 and 2 investigations showing the feasibility of RIT in different primary settings are available [34–39]. Data on the combination of ReRT and IT so far is limited to case reports: While Finazzi et al. paused pembrolizumab during a second course of re-irradiation with of a HNSCC relapse [40], Bonomo et al. continued nivolumab during irradiation of two priorly unirradiated lesions in

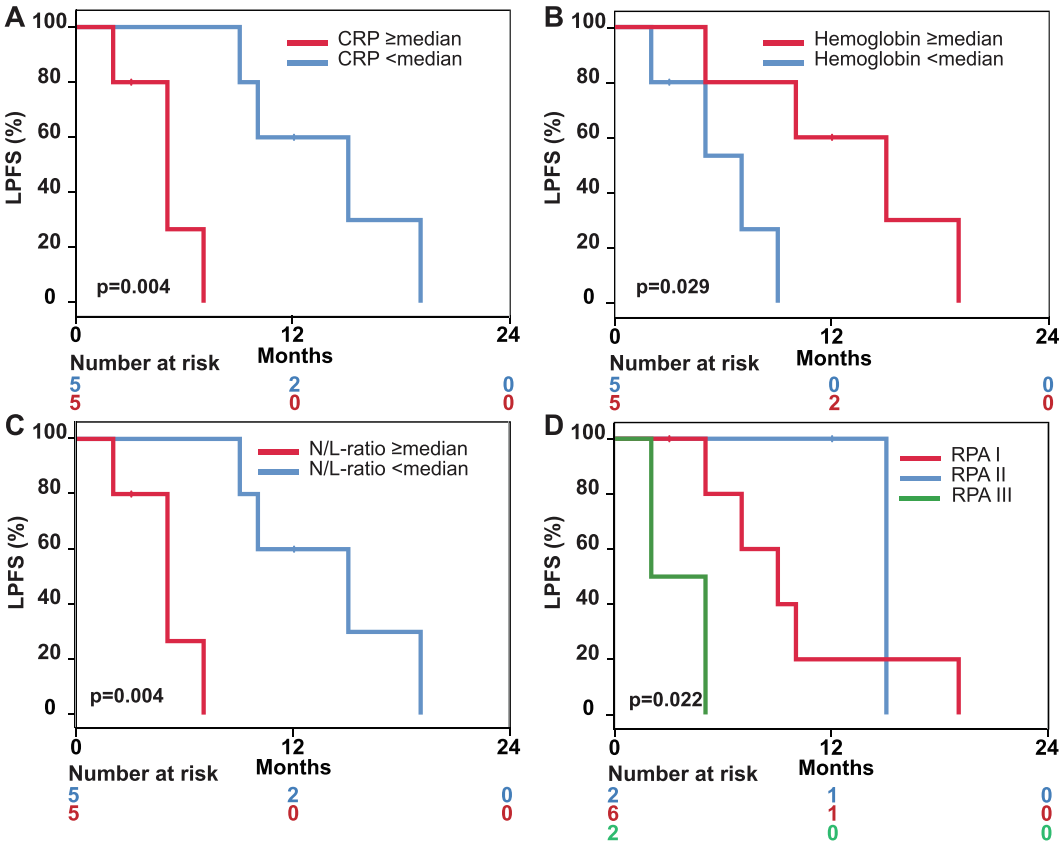

Fig. 3. Impact of pre-treatment clinical factors on local progression-free survival following re-irradiation. A: Impact of pre-treatment CRP level on local progression-free survival following re-irradiation; B: Impact of pre-treatment hemoglobin level on local progression-free survival following re-irradiation; C: Impact of pre-treatment N/L ratio on local progression-free survival following re-irradiation; D: Impact of pre-treatment RPA class on local progression-free survival following re-irradiation. Abbreviation: CRP – C-reactive protein, N/L ratio – Neutrophil granulocytes / lymphocytes ratio, RPA – Recursive partitioning analysis class, LPFS – Local progression-free survival.

an oligoprogressive setting. Altogether, these data underscore the feasibility of the combination of RT and IT for head and neck cancer and are in accordance with our observations, where no unexpected side effects occurred. Grade 3 irAE occurred in 20% of our patients in terms of hypothyreosis in both cases. All patients had normal thyroidea stimulating hormone (TSH) levels prior to ReRT and start of nivolumab administration. Therefore, a connection with the first irradiation seems unlikely. However, the possibility of thyroid toxicity due to ReRT cannot ultimately be ruled out. Still, this rate is higher than reported in the Checkmate 141 trial and could otherwise be attributed to bias as the low patient numbers [14]. The concept of our study is actually being tested in a prospective phase II trial by the Emory University, Atlanta, USA. The trial is currently recruiting patients to receive intensity-modulated ReRT with concurrent and maintainance nivolumab for HNSCC without distant metastases (ClinicalTrials.gov Identifier: NCT03521570).

Accurate patient selection remains challenging for such a complex and toxic treatment. Besides emerging biological markers predicting the response to IT such as PD-L1 status, tumor mutational burden (TMB) or T-cell density, data on prognostic clinical factors remain scarce so far [41]. Regarding ReRT, clinical considerations as proposed by several authors can guide patient selection [42,43]. In our cohort, both LPFS and OS were only influenced by RPA classification of patients introduced by Ward et al. to select patients for ReRT with concurrent CHT [17]. Furthermore, elevated CRP levels and higher NLR were associated with impaired LPFS without impact on OS. Increased pre-treatment NLR as a marker of systemic inflammatory response has been associated before with impaired outcome in several cancer types [44] and HNSCC [45]. The same has been shown for CRP in 226 patients undergoing primary surgery for oropharyngeal carcinoma [46]. Also, in accordance to the literature, decreased HB levels were associated with impaired LPFS in this cohort [47].

This study has limitations: firstly, the retrospective design, secondly the very low number of patients, thirdly the fact that all patients could be not clearly defined as being platinum-refractory, and fourthly the relatively short follow-up. Nevertheless, this is the first report of combined re-irradiation and immunotherapy for head and neck cancer.

5. Conclusion

The combination of a second course of radiotherapy and nivolumab for locally recurrent squamous cell carcinoma of the head and neck appears to be feasible and was not associated with unexpected toxicities. RIT might offer a potentially curative treatment option for carefully selected, pre-irradiated patients ineligible for surgery. Superiority of RIT over systemic treatment alone has to be evaluated in prospective, randomized clinical trials.

Disclosure of interest

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Appendix A. Supplementary data

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